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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/371,354	08/10/1999	STEPHEN DONOVAN	17310	9137

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STEPHEN DONOVAN
LEGAL DEPTALLERGAN INC TOWER TWO 7TH FLR
2525 DUPONT DRIVE
IRVINE, CA 926239534

EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	21

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/371,354	DONOVAN, STEPHEN	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *7,15-17,37 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,15-17,37 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 20 February 2003 (Paper No. 19) has been entered in full. Claims 7 and 38 are amended.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 7, 15-17, and 37-38 are under consideration in the instant application.

Claim Rejections - 35 USC § 112

1. Claims 7, 15-17, and 37-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 7, 15-17, and 37-38 are directed to a method for treating bradycardia comprising intrapericardial injection of a botulinum toxin to the sinoatrial (SA) node or to the atriovenctricular (AV) node of a heart of a patient with bradycardia to treat bradycardia. The claims also recite that botulinum toxin is botulinum toxin A and is locally administered to the heart in an amount between 0.01 U/kg and 35 U/kg, between 0.1 U/kg and 30 U/kg, between 1U/kg and 25 U/kg. The basis for this rejection is set forth in previous Office Actions (Paper No. 18, 18 October 2002; Paper No. 11, 25 February 2002; Paper No. 6, 05 July 2001).

Applicant's arguments (Paper No. 19, 20 February 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) At pg 6 of the Response, Applicant asserts that medical researchers have demonstrated that *in vivo* administration of a botulinum toxin to the SA node of a mammal's heart does indeed treat bradycardia (Tsuboi et al., Jpn J Pharmacol 89(3): 249-254, 2002). Applicant argues that Tsuboi et al. demonstrate that administration of a botulinum toxin to the sinoatrial node of a dog heart blocks parasympathetic mediated bradycardia.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the canine model system of Tsuboi et al. is not predictive of the scope of the instant claims. For instance, Tsuboi et al. disclose that a decrease in heart rate is induced by stimulation of the preganglionic parasympathetic nerves in the heart by electrical stimulation (abstract; pg 250, ¶ 4). However, the state of the art teaches that bradycardia in patients is caused by either intrinsic dysfunction of or damage to the conduction system or by the response of normal tissues to extrinsic factors (Mangrum et al. N Eng J Med 342(10): 703-709, 2000; see pg 703, ¶ 1; pg 704, col 2 through pg 705; Table 1). However, there is no guidance in the specification or prior art indicating that electrical stimulation of the preganglionic parasympathetic nerves of the heart is a model system for bradycardia. Therefore, Tsuboi et al.'s treatment of *electrically stimulated* preganglionic parasympathetic nerves of the canine heart with botulinum toxin A is not predictive of treating bradycardia in general with botulinum, wherein the bradycardia may be caused by numerous intrinsic, extrinsic, or damaging factors, such as collagen vascular diseases, surgical trauma, drugs, hypothermia, etc. (Mangrum, Table 1).

Furthermore, the canine experiments of Tsuboi et al. are not commensurate in scope with the instant claims because Tsuboi et al. disclose injecting botulinum A into the sinoatrial (SA) fat pad, while the claims recite intrapericardial injection of a botulinum toxin to the SA node or AV

node of the heart. Tsuboi et al. (Am J Physiol Heart Circ Physiol 279: H1201-H1207, 2000; pg H1201, col 1) indicate that parasympathetic ganglionic cells exist in the fatty tissue overlying the right atrial junction of the right pulmonary veins in the heart, called the SA fat pad (pg 249, ¶ 2, col 2). Mangrum et al. state that the sinus node is a collection of specialized cells located in the sulcus terminalis at the junction of the superior vena cava and the right atrium (pg 703, col 2). Therefore, the state of the art is such that the SA node and AV node are specialized clusters of cells in the heart which differ from fatty tissue of the SA fat pad, which contains parasympathetic ganglionic cells. One skilled in the art would not be able to predict that injection of botulinum into the SA node or AV node would treat bradycardia based on the 2002 Tsuboi et al. reference because the cited reference and the instant claims inject botulinum toxin into different parts of the heart, which may produce different effects in the subject.

The 2002 Tsuboi et al. reference relied upon by Applicant also does not teach injection of any botulinum toxin into the AV node (or even the AV fat pad) of the heart. Tsuboi et al. specifically indicate that botulinum toxin A is injected into the SA fat pad only (abstract;; pg 249, ¶ 2; pg 250, col 2). Therefore, the skilled artisan still must resort to trial and error experimentation to inject all possible types of botulinum toxin into the AV node to treat bradycardia.

Additionally, the canine model system of the 2002 Tsuboi et al. reference is not predictive of the scope of the instant claims because Tsuboi et al. teaches administering botulinum toxin A, while the claims recite the administration of any botulinum toxin. Undue experimentation is required by one skilled in the art to determine the optimal type of botulinum toxin to treat bradycardia. Tsuboi et al. also teaches only administering 20-25 mouse units of

botulinum toxin A to dogs who weighed between 15-28 kg (pg 250, ¶ 2, ¶ 5). Accordingly, the dogs in Tsuboi et al. are administered between 0.71 U/kg and 1.7 U/kg of botulinum toxin A (for example, 25units/15 kg and 20 units/28kg). Although these dosages overlap with the dosage ranges recited in claims 15-17, the Tsuboi et al. dosages are low in comparison with the 25 U/kg-35 U/kg dosages that are recited in the claims. The specification of the instant application does not teach the skilled artisan a specific safe dosage or duration of treatment of any botulinum toxin to the SA node or AV node of the heart. Undue experimentation would be required of the skilled artisan to determine the optimal dose of botulinum toxin to be administered to every patient without damaging the heart.

(ii) Applicant asserts that the 20 February 2002 declaration from Dr. Mitchell Brin establishes that Dr. Brin is an expert of long standing in the therapeutic use of botulinum toxin. Applicant contends that according to the declarant's opinion, a patient with bradycardia, vagal nerve inhibition and hence an increase in heart rat can be accomplished by intrapericardial injection of a botulinum toxin to the SA node or to the AV node of the heart without undue experimentation. Applicant indicates the Brin declaration states that matters such as the specific time period in which the toxin should be administered or for how long, and the specific dosage of the botulinum toxin to use entail consideration of factors such as the patient's size, weight, age, and disease severity which factors are routine considerations determined on a patient by patient basis by the treating physician who has knowledge of the therapeutic use of a botulinum toxin. It is noted that the Brin declaration also relies upon Tsuboi et al. (2002) as purported evidence to

indicate that the administration of a botulinum toxin to the SA node of a dog heart blocks parasympathetic mediated bradycardia.

Applicant's arguments have been fully considered but are not found to be persuasive. The declaration under 37 CFR 1.132 filed 20 February 2003 (Paper No. 20) is insufficient to overcome the rejection of claims 7, 15-17, and 37-38 based upon lack of enablement under 35 U.S.C. § 112, first paragraph, as set forth in the previous Office Actions. Although Dr. Brin has a distinguished career and was one of the first investigators to examine the use of botulinum toxin for treatment of medical disorders, the declaration filed in the instant case is based upon opinion. The contradictory factual evidence in the Tsuboi et al. reference outweighs the opinion of the declarant. For example, as discussed in part (i) above, Tsuboi et al. teaches a canine model system that is not predictive of the scope of the claims for several reasons. Tsuboi et al. utilize *electrically stimulated* preganglionic parasympathetic nerves of the canine heart to induce bradycardia, which may be physiologically different from bradycardia normally induced by various intrinsic, extrinsic, or damaging factors that normally induce bradycardia. Tsuboi et al. also do not teach treatment of bradycardia by administration of any botulinum toxin to the AV node, which is required by the claims. Tsuboi et al. specifically inject botulinum toxin A into the SA fat pad, rather than any non-specific botulinum toxin into the SA node or AV node. Tsuboi et al. utilize much smaller amounts of botulinum toxin A than the high range dosages recited in the claims. It is also noted by the Examiner that Dr. Brin is currently employed by Allergan, the assignee of the instant application, and therefore is a party of interest in the outcome of the case.

Proper analysis of the Wands factors has been provided in previous Office Actions. Due to the large quantity of experimentation necessary to treat bradycardia by administering any

botulinum toxin to the SA node or AV node of the heart and to determine the dosage and safety of botulinum toxin and the timing and duration of administration, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the state of the art (see Tsuboi et al.), and the unpredictability of the effects of any botulinum toxin on a subject (see discussion), undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elyabeth C. Kemmerer

BEB
Art Unit 1647
June 25, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER